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371 Application As-Filed

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UNITED STATES PATENT AND TRADEMARK OFFICE
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Miscellaneous

10

Level - 2
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FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	220902US0PCT
U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	10/070439
INTERNATIONAL APPLICATION NO.	PCT/JP99/05217
INTERNATIONAL FILING DATE	24 September 1999
PRIORITY DATE CLAIMED	None

TITLE OF INVENTION
INHIBITORY SUBSTANCE OF PPAR ALPHA AND PPAR GAMMA

APPLICANT(S) FOR DO/EO/US
Koji MURAKAMI et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail
23. ☒ Other items or information:
    Form PTO-1449

JC10 Rec'd PCT/PTO 19 MAR 2002

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/070439	PCT/JP99/05217	220902US0PCT

24. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	$1040.00
☒	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	$890.00
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$740.00
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$710.00
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	$100.00

ENTER APPROPRIATE BASIC FEE AMOUNT =	$890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	$130.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	6 - 20 =	0	x $18.00	$0.00	
Independent claims	4 - 3 =	1	x $84.00	$84.00	
Multiple Dependent Claims **(check if applicable)**.			☐	$0.00	
TOTAL OF ABOVE CALCULATIONS =				$1,104.00	
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				$0.00	
SUBTOTAL =				$1,104.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				$0.00	
TOTAL NATIONAL FEE =				$1,104.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				$0.00	
TOTAL FEES ENCLOSED =				$1,104.00	
				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of **$1,104.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **15-0030** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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REGISTRATION NUMBER

March 19 2002
DATE

SPECIFICATION

Title of the invention

Inhibitory substance of PPARα and PPARγ

Technical field

The present invention relates to an application of fatty acid CoA thioester found out as an active inhibitory substance against peroxisome proliferator-activated receptor α and γ (hereinafter referred to as PPARs) to the assay of medicinal drug, and a use of fatty acid CoA thioester for medicinal drug.

Background technologies

The peroxisome proliferator-activated receptor (PPAR) is a transcription factor to be activated when a ligand binds to the ligand-binding domain at the side of C-termini, and one of the nuclear receptor superfamily having glucocorticoid, estrogen, thyroxine and vitamin D as ligands (Keller H. et al: Trends Endocrinol. Metab. (1993) 4, 291-296). So far, three types of isoforms of α form, γ form and δ form have been identified as PPARs, and the expression tissues and the functions are different respectively (Braissant O. et al: Endocrinology (1996) 137, 354-366). The PPARα is highly expressed in the tissues with high catabolic activity of fatty acids such as liver, kidney and heart. The PPARγ is divided into PPARγ1 and PPARγ2 as two types of isoforms with the sides of different N-termini through the selection of

promoters; PPARγ1 is expressed in the relatively widespread tissues and PPARγ2 is highly expressed mainly in the adipose tissue. The PPARδ is distributed in the widespread tissues.

The PPARα binds to promoter domain of key enzymes concerning in the lipid catabolism system such as acyl-CoA synthase existing in the cytosol, acyl-CoA dehydrogenase and HMG-CoA synthase existing in the mitochondria and acyl-CoA oxidase existing in the peroxisome of liver (Schoonjans K. et al: J. Lipid Res.(1996) 37, 907-925). From the analysis of PPARα-deficient mice, it is being considered that the PPARα plays an important role for the energy acquisition in starvation state, that is, oxidation of fatty acid and formation of ketone body in liver (Kersten S. et al: J. Clin. Invest. (1999) 103, 1489-1498).

On the other hand, it is known that the PPARγ concerns deeply in the differentiation of adipocytes (Forman BM. et al: Cell (1995) 83, 803-812). Thiazolidinedione derivatives such as troglitazone, rosiglitazone (BRL-49,653) and pioglitazone are new therapeutic drugs of type 2 diabetes with a unique function that improves the insulin resistance being one of pathogenic factors of diabetes, and, in recent years, it has been revealed that those drugs are agonists against PPARγ (Lehmann JM. et al: J. Biol. Chem. (1995) 270, 12953-12956). It is being considered that the PPARγ plays an important role for the energy storage in organisms. However, the function of PPARδ is not very understood compared with α form or γ form.

As described above, for the agonists against PPAR, glitazone-classed drugs are well known. Also, it is reported

that natural or endogenous-produced saturated and unsaturated fatty acids, certain kinds of eicosanoid, oxidized fatty acids, etc. are agonists against PPAR (Forman BM. et al: Proc. Natl. Acad. Sci. USA (1997) 94, 4312-4317).

On the other hand, it is the status quo that the inhibitory substance and antagonist against PPAR are little known. Only 2,4-thiazolidinedione derivatives are known as the antagonists against PPARγ (Oberfield J. L. et al: Proc. Natl. Acad. Sci. USA (1999) 96, 6102-6106).

As the use of antagonist against PPARγ, application to antiobesity drug is disclosed (WO97/10813), not getting however to the discovery of antagonistic substance.

Much less, the inhibitory substance or antagonist against PPARα is not known at all.

Up to this time, no antagonist against PPARγ and PPARα has been discovered even in the natural or endogenous substances.

The purpose of the invention is to create a very high-novelty medicinal drug for the carbohydrate and lipid metabolism-related diseases by finding out an inhibitory substance or antagonist against PPARα and PPARγ.

Disclosure of the invention

When the inventors were implementing studies on the participation of PPAR in the induction of insulin resistance, they have found, to their surprise, that certain fatty acid CoA thioester forms being the metabolites of fatty acids have inhibitory function against PPARα and PPARγ, leading to the completion of the invention.

Namely, through competition binding experiments using tritium-labeled form of KRP-297 (Murakami K. et al: Diabetes (1998) 47, 1841-1847) being a dual agonist against PPARα and PPARγ, it has been found that different fatty acid CoA thioesters bind well to the ligand-binding domains of PPARα and PPAR γ, thus making it clear that they are ligands of both α and γ receptors.

In addition, the fatty acid CoA thioesters dose-dependently inhibited the binding activity on the conjugate formation between ligand-binding domains of PPARα and PPARγ and steroid receptor coactivator (SRC-1). Consequently, the fatty acid CoA thioesters clarified themselves to be inhibitory substances of PPARα and PPARγ.

According to the invention, the fatty acid CoA thioester can be used for the exploration of creation of medicinal drug and the assay tools, as an inhibitory substance or antagonist against PPARα and PPARγ, which makes it useful.

Namely, the fatty acid CoA thioester in which fatty acid group is myristoyl, palmitoyl, stearoyl, oleoyl, linoleoyl or arachidonoyl can be used for the creation of medicinal drug as an inhibitory substance against PPARα, and the fatty acid CoA thioester in which fatty acid group is myristoyl, palmitoyl, stearoyl, oleoyl, linoleoyl or arachidonoyl can be used for the creation of medicinal drug as an inhibitory substance against PPARγ.

Furthermore, it is also possible to use the fatty acid CoA thioester itself as a medicinal drug. Fields of medicinal drug are as follows:

1) Application as an antagonist of PPARα

It is known that, in the case of critical diabetes, mainly type 1 diabetes, the diabetic ketoacidosis can often occur as an acute complication. The diabetic ketoacidosis clinically assumes dehydration, disorder of consciousness, depressed blood pressure, tackycardia, respiratory stimulation, Kussmaul's large respiration and acetone odor of exhalation (Keller U. et al: Diabetologia (1986) 29, 7-77). From the fact that PPARα plays an important role for the oxidation of fatty acid and the formation of ketone body in liver, it is expected that the antagonist of PPARα can inhibit them, hence it is useful for the therapy of diabetic ketoacidosis.

2) Application as an antagonist of PPARγ

Obesity is a risk factor for diabetes, hyperlipidemia, hypertension, ischemic heart disease, etc., hence the prevention and therapy thereof are very important subjects clinically. The PPARγ plays an important role for the differentiation of adipocytes. Actually, the thiazolidinedione derivatives, PPARγ agonists, have differentiation-inducing function of adipocytes, and it is reported that they increase the number of adipocytes and the weight of adipose tissue (Piet De Vos et al: J. Clin. Invest. (1996) 98, 1004-1009). While the thiazolidinedione derivatives have usefulness as the therapeutic drugs of diabetes, they induce the differentiation of adipocytes, hence the potential for promoting the obesity is also feared. Also, it is reported that the expression level of leptin known as an antiobese factor is deprssed through the

administration of thiazolidinedione derivatives (Zhang E. et al: J. Biol. Chem. (1996) 271, 9455-9459). Based on these backgrounds, the antagonist of PPARγ suppresses the differentiation of adipocytes and, at the same time, it increases the expression level of leptin, thereby the potential as an antiobesity drug is expected.

Best embodiment to put the invention into practice

In following, the invention will be illustrated based on concrete examples, but the invention is not confined to these examples.

Example 1. Measurement of binding activity to PPARα and PPARγ

Competition experiments using tritium-labeled form of KRP-297 (Murakami K. et al: Diabetes (1998) 47, 1841-1847) being a dual agonist against PPARα and PPARγ were implemented. Proteins (6×His-hPPARs LBD) tagged 6-copy histidine to the side of N-termini in the ligand-binding domains of human-type PPARα and PPARγ were expressed in Escherichia coli, respectively, and purified through a nickel column. 6×His-hPPARs LBD protein and 100nM [3H]KRP-297 (27Ci/mmol) were incubated for 30 minutes at 25℃ in 50 mM Tris-HCl buffer (pH 7.4) containing 50mM KCl and 10mM dithiothreitol in the presence or absence of testing compound (fatty acid CoA thioester, from Sigma Co.). Thereafter, [^{3}H]KRP-297 bound to protein was separated through Sephadex G25 column and the radioactivity was measured with liquid scintillation counter.

As control drugs for the binding activity against PPARγ, BRL-49,653 (Willson TM. et al: J. Med. Chem. (1996) 39, 665-

668) and 15-deoxy- $\Delta^{12,14}$-prostaglandin J_2 (from Cayman Chemical Co.) were used and, as a control drug for the binding activity against PPARα, 8(S)-hydroxyeicosatetraenoic acid (from Cayman Chemical Co.) was used.

As a result, it became clear that the thioester of myristic acid CoA, palmitic acid CoA, stearic acid CoA, oleic acid CoA, linoleic acid CoA or arachidonic acid CoA was ligand of PPARα and PPARγ (Table 1).

[Table 1]

Binding of fatty acid CoA to the ligand-binding domain of PPAR

	PPARα	PPARγ
BRL-49,653		99%
15-Deoxy- $\Delta^{12,14}$-prostaglandin J_2		93%
8(S)-Hydroxyeicosatetraenoic acid	99%	
Myristoyl CoA	70%	45%
Palmitoyl CoA	83%	72%
Stearoyl CoA	94%	89%
Oleoyl CoA	95%	52%
Linoleoyl CoA	92%	59%
Arachidonoyl CoA	54%	46%

Data represent average value of 3 experiments ± standard error.

Example 2. Measurement of conjugate-forming activity between PPARs LBD and SRC-1

[35S]methionine-labeled form of SRC-1 containing 2-copy of LXXLL motif was prepared in vitro (TNT®, Promega Co., Madison, WI). 6× His-hPPARs LBD protein was incubated for 60 minutes at 4℃ in 50mM Tris-HCl buffer (pH 7.4) containing 50mM KCl and 1mM dithiothreitol and 0.1% bovine serum albumin in the presence or absence of testing compound. Thereafter, 2mg of anti-6×His antibody (QIAGEN Co., Germany) were added and the mixture was incubated for 60 minutes at 4℃. Successively, 20ml of protein G Sepharose (Falmasia·Biotech Co., Sweden) were added and the mixture was incubated for 60 minutes at 4℃. After washed thrice by centrifugation, protein G Sepharose was dissolved with 20ml of SDS-sample buffer, 20% SDS-PAGE, and then [35S]SRC-1 was detected by means of autography.

As a result, linoleic acid CoA thioester dose-dependently inhibited the conjugate formations of SRC-1 due to ligands of PPARα, KRP-297 and linoleic acid, and also dose-dependently inhibited the conjugate formations of SRC-1 due to ligands of PPARγ, BRL-49,653 and linoleic acid (Table 2).

[Table 2]
Inhibition of fatty acid CoA on the conjugate formation between PPARs ligand-binding domain and SRC-1

		Human PPARα		Human PPARγ	
		KRP-297 linoleic acid		BRL-49653 linoleic acid	
		30μM	30μM	30μM	30μM
Linoleoyl CoA	0μM	6.1±1.7	5.3±1.9	4.8±0.7	4.5±0.7
Linoleoyl CoA	3μM	5.5±1.5	6.1±2.2	4.9±0.6	4.2±0.3
Linoleoyl CoA	10μM	4.4±0.8	2.4±0.8	4.8±1.9	2.7±1.1
Linoleoyl CoA	30μM	1.4±0.1	1.2±0.4	1.5±0.5	1.9±0.8
Linoleoyl CoA	100μM	0.9±0.3	0.9±0.3	1.0±0.1	1.3±0.4

Data represent average value of 3 experiments ± standard error.

Utilizability in the industry

When studies on the participation of PPAR in the induction of insulin resistance were implemented, it was found that certain fatty acid CoA thioester forms being the metabolites of fatty acids had inhibitory function against PPARα and PPARγ.

As a result, the fatty acid CoA thioester in which fatty acid group is myristoyl, palmitoyl, stearoyl, oleoyl, linoleoyl or arachidonoyl can be used for the creation of medicinal drug as an inhibitory substance against PPARα, and the fatty acid CoA thioester in which fatty acid group is myristoyl, palmitoyl, stearoyl, oleoyl, linoleoyl or arachidonoyl can be used for the creation of medicinal drug as an inhibitory substance against PPARγ.

Furthermore, it is also possible to use the fatty acid CoA

thioester itself as a medicinal drug concerning in the carbohydrate and lipid metabolism-related diseases.

SCOPE OF THE CLAIM

1. Application of fatty acid CoA thioester as an inhibitory substance against PPARα.
2. Application of fatty acid CoA thioester as an inhibitory substance against PPARγ.
3. Application of fatty acid CoA thioester of Claim 1, wherein the fatty acid group is myristoyl, palmitoyl, stearoyl, oleoyl, linoleoyl or arachidonoyl, as an inhibitory substance against PPARα.
4. Application of fatty acid CoA thioester of Claim 2, wherein the fatty acid group is myristoyl, palmitoyl, stearoyl, oleoyl, linoleoyl or arachidonoyl, as an inhibitory substance against PPARγ.
5. A therapeutic agent for the diabetic ketoacidosis, characterized by containing fatty acid CoA thioester.
6. A therapeutic agent for the obesity, characterized by containing fatty acid CoA thioester.

SUMMARY

The invention creates a very high-novelty medicinal drug for the carbohydrate and lipid metabolism-related diseases by finding out an inhibitory substance or antagonist against PPAR α and PPARγ, and relates to an application of fatty acid CoA thioester that was found out as an active inhibitory substance against peroxisome proliferator-activated receptor α and γ (hereinafter referred to as PPARs) to the assay of medicinal drug, and a use of fatty acid CoA thioester for medicinal drug.

Declaration, Power Of Attorney and Petition

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

PPARα and PPARγ inhibitors

the specification of which

☐ is attached hereto.

☐ was filed on _____ as

Application Serial No. _____

and amended on _____.

☒ was filed as PCT international application

Number PCT/JP99/05217

on September 24, 1999,

and was amended under PCT Article 19

on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

We (I) hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application Number) (Filing Date)

(Application Number) (Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	Filing Date	Status (pending, patented, abandoned)

And we (I) hereby appoint: Norman F. Oblon, Reg. No. 24,618; Marvin J. Spivak, Reg. No. 24,913; C. Irvin McClelland, Reg. No. 21,124; Gregory J. Maier, Reg. No. 25,599; Arthur I. Neustadt, Reg. No. 24,854; Richard D. Kelly, Reg. No. 27,757; James D. Hamilton, Reg. No. 28,421; Eckhard H. Kuesters, Reg. No. 28,870; Robert T. Pous, Reg. No. 29,092; Charles L. Gholz, Reg. No. 26,395; Vincent J. Sunderdick, Reg. No. 29,004; William E. Beaumont, Reg. No. ~~30,996;~~ Robert F. Gnuse, Reg. No. 27,295; Jean-Paul Lavalleye, Reg. No. 31,451; Stephen G. Baxter, Reg. No. 32,884; Martin M. Zoltick, Reg. No. 35,745; Robert W. Hahl, Reg. No. 33,893; Richard L. Treanor, Reg. No. 36,379; Steven P. Weihrouch, Reg. No. 32,829; John T. Goolkasian, Reg. No. 26,142; Richard L. Chinn, Reg. No. 34,305; Steven E. Lipman, Reg. No. 30,011; Carl E. Schlier, Reg. No. 34,426; James J. Kulbaski, Reg. No. 34,648; Richard A. Neifeld, Reg. No. 35,299; J. Derek Mason, Reg. No. 35,270; Surinder Sachar, Reg. No. 34,423; Christina M. Gadiano, Reg. No. 37,628; Jeffrey B. McIntyre, Reg. No. 36,867; and Paul E. Rauch, Reg. No. 38,591; our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C., whose Post Office Address is: Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

30

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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NAME OF FIFTH JOINT INVENTOR

Signature of Inventor

Date

Residence:

Citizen of:
Post Office Address:

United States Patent & Trademark Office

Office of Initial Patent Examination -- Scanning Division

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Application deficiencies found during scanning:

☑ Page(s) 6 of drawing (Document title) ~~were~~ not present for scanning.

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